Updates in Primary Bone Tumors

Current Challenges and New Opportunities in Cytopathology

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KEYWORDS

• Aneurysmal bone cyst • Chondroblastoma • Chondrosarcoma • Giant cell–rich
• Giant cell tumor of bone • Notochordal tumors • Chordoma • Fine-needle aspiration

Key points

- Collaboration within a multidisciplinary team is still the fundamental approach to establishing a correct and/or clinically relevant diagnosis of primary bone tumors.
- The identification of histone 3.3 mutations in giant cell tumor of bone and chondroblastoma has led to the development of diagnostically useful mutation-specific markers, H3G34W and H3K36M, which can improve the diagnostic accuracy among giant cell–rich neoplasms, especially in needle biopsy samples.
- Recurrent molecular alterations have been found, including *IDH1/2* mutations in both benign and malignant cartilaginous tumors and *HEY1-NCOA2* fusion in mesenchymal chondrosarcoma. Molecular studies may help in some but not all difficult differential diagnoses of chondrosarcomas on needle biopsy samples.
- Bimorphic bone tumors, such as mesenchymal chondrosarcoma, dedifferentiated chondrosarcoma, and dedifferentiated chordoma, pose significant diagnostic pitfalls in fine-needle aspiration biopsies due to potential sampling errors.
- An additional advantage of fine-needle aspiration over surgical biopsy for bone tumors is the ability to obtain samples with high-quality DNA and RNA for molecular/genetic testing without the damage of decalcification.

ABSTRACT

The review summarizes the current diagnostic challenges in fine-needle aspiration of primary bone tumors, with focus on the application of new molecular and immunohistochemical techniques in the diagnosis of giant cell–rich neoplasms, chondrosarcomas, and notochordal tumors.

OVERVIEW

Evaluation of primary bone tumors by minimally invasive biopsy techniques, such as fine-needle aspiration (FNA) and core needle biopsy (CNB), remains one of the most challenging areas in surgical pathology, particularly in cytopathology.[1,2] The practice has been limited to a few large tertiary centers because of the uneasiness of general cytopathologists with primary bone tumors, which are uncommon and require a high level of collaboration within a multidisciplinary team to make a correct diagnosis.[3] Recent advances in understanding the underlying molecular genetics in certain bone tumors not only have increased knowledge of their pathogenesis but also led to the development of novel molecular and surrogate immunohistochemical (IHC) diagnostic tools. A new era of using FNA material for the judicious application of ancillary

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studies to supplement the traditional approach of integration of clinical and imaging characteristics for the diagnosis of primary bone tumors is expected to emerge in the horizon. General discussion of cytologic diagnosis of bone tumors is beyond of scope of this focused review, and readers are directed to prior excellent reviews[1,2] and book chapters.[3,4] In this review, entities with recent molecular advances and their respective opportunities for cytopathologic practice are selected for discussion. Relevant updates in the current 2013 World Health Organization (WHO) classification of tumors of soft tissue and bone are included.[5]

GIANT CELL–RICH TUMORS

Giant cell–rich tumors represent a broad group of tumors and tumor-like lesions, which are characterized morphologically by the presence of numerous osteoclasts or osteoclast-like giant cells. A summary of differential diagnosis of giant cell–rich tumors is provided in **Table 1**.

GIANT CELL TUMOR OF BONE

Giant cell tumor (GCT) of bone is a locally aggressive neoplasm that has a predilection for young adults with a mature skeleton and usually arises in the epiphyseal-metaphyseal region of long bones around the knee. GCT of bone represents approximately 5% of primary bone tumors and 20% of benign bone tumors. The treatment options include surgical curettage and receptor activator of nuclear factor κB (RANK) ligand (RANKL) inhibitors, such as denosumab.[6] Up to one-third of patients recur after treatment by curettage, and fewer than 5% of cases show malignant transformation, either occurring de novo or developing during recurrence. Classically, GCT of bone on image studies shows an eccentric, large, and pure lytic intramedullary lesion with sharp borders in the epiphyseal-metaphyseal region of distal femur. Aspirates are typically cellular and characterized by a dual cell population: mononuclear spindled or ovoid cells and admixed with numerous large osteoclast-like giant cells containing 20 to 50 (or more) nuclei (**Fig. 1**). In the presence of these characteristic radiographic and cytologic features, the diagnosis of GCT by FNA can be straightforward. Significant clinical, radiologic, and morphologic overlap exists, however, among many benign and malignant giant cell–rich neoplasms, posing considerable diagnostic challenges, especially in FNA/CNB samples.[2,7]

The main diagnostic challenges of GCT of bone include (1) separating from other giant cell–rich benign neoplasms/lesions, such as solid aneurysmal bone cyst (ABC), chondroblastoma, chondromyxoid fibroma, GCT of Paget disease, nonossifying fibroma, giant cell lesion of the small bones (GCLSB) (giant cell reparative granuloma), and brown tumor of hyperparathyroidism; (2) distinguishing giant cell–rich osteosarcoma from GCT of bone with atypical features (cytologic atypia, necrosis, and mitosis); and finally (3) recognizing denosumab-treated GCT of bone, which shows markedly diminished osteoclast-like giant cells and increased fibrosis and hyalinization.[6,8]

Main Diagnostic Challenges of GCT of Bone

- To separate GCT of bone from other giant cell–rich benign neoplasms/lesions
- To distinguish giant cell–rich osteosarcoma from GCT of bone with atypical features
- To recognize denosumab-treated GCT of bone

One of the updates in the 2013 WHO classification was separating GCT of bone from GCLSB.[5,9] GCLSB, along with similar lesions arising in jaw bones, is also called giant cell reparative granuloma in practice. Giant cells clustering around the areas of hemorrhage, a key histologic feature in GCLSB, is usually absent in FNA cytology preparations.[10] In fact, the cytomorphologic features of GCT of bone, GCLSB, GCT of Paget disease, and brown tumor of hyperparathyroidism are usually indistinguishable.[2,3,10,11] The presence of benign fibrous histocytoma-like areas in GCT of bone mimics nonossifying fibroma. The cyst formation in GCT of bone makes distinguishing it from primary ABC difficult.[7,12] Considering the differences in recurrence rates, prognoses, and treatment strategies, it is important to distinguish GCT of bone from its benign giant cell–rich mimics. Definitive distinction, however, is not always possible, even with correlation of clinical and radiologic findings, especially when a tumor arises at unusual anatomic sites and/or shows atypical morphologic features (**Fig. 2**). In such settings, traditionally, a descriptive diagnosis, such as "giant cell–rich neoplasm" is often given with a list of differential diagnoses.

The recent discovery of recurrent somatic driver mutations in *H3F3A* (located at 1q42.12) and *H3F3B* (located at 17q25.1) in the majority GCTs of bone and chondroblastomas, respectively,[13] has forever reshaped the diagnostic field of giant cell–rich neoplasms. *H3F3A* and *H3F3B* have different DNA sequences but both encode replication-independent histone proteins (H3.3) of identical amino acid sequences. The most